



User manual for Bayesian BMD

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1 INTRODUCTION

Bayesian BMD is an online application developed to run Bayesian Benchmark Dose Modelling analyses on supplied data. It allows to estimate the dose that corresponds with the benchmark response of interest. The estimated benchmark dose (BMD) is reported along with its lower and upper confidence bounds. When fitting a set of models, a weighted average of the model-specific BMD estimates can be obtained. The application uses the R-package BMABMDR to perform data preparation, model fitting, model averaging and plotting. As such, the performed analyses in the application are run in R.

1.1 Installation

The application is available at <https://r4eu.efsa.europa.eu/app/bmdbayesian>, provided you have an account.

Alternatively, the application can be run locally by installing the package on your computer.

Prior to the installation, please make sure that the proxy is configured properly to access the internet from EFSA premises:

```
library(httr)
set_config(use_proxy(url="tmgproxy", port=8080, username="user",
                    password="password"))
```

To run the application locally, all required package dependencies need to be installed. By setting function argument `installDependencies` of function `runShiny()` to `TRUE`, the application will be launched after all dependent packages have been installed. If all dependencies have been installed once, the app can be run via `runShiny()` without any function arguments.

```
install.packages("path_to_file/bmaBmdrUI_versionNumber.tar.gz",
                repos = NULL, type = "source")

# For example:
# install.packages("/home/wverlinden/git/bmdBayesian/bmaBmdrUI_0.0.10.tar.gz",
# repos = NULL, type = "source")

library(bmaBmdrUI)

# First use
runShiny(installDependencies = TRUE)

# Later use
runShiny()
```

Figure 1: Start screen for bmaBmdrUI.

1.2 Getting started

The start screen of the online application is shown in Figure 1.

Using the tab pages, one can switch between:

- **Data:** Load and specify the data to be analyzed.
- **Fit Models:** Fit benchmark dose models using BMABMDR and obtain a summary of the analysis.
- **Advanced Plotting:** Provides the user the option to plot and download the prior and posterior distribution of parameter estimates. When multiple responses or analyses have been performed, the user can select the plots over different responses and analysis scenario's by adding a new row of inputs to the input panel

After the analysis is performed, a Word document with summarized results can be obtained by pushing the button **Download report** at the top left of the page.

New issues can be reported by clicking **Report new issue** after which a window will be opened for the user to describe the issue via e-mail.

1.3 App functionality

The application is built in a modular way. This can be seen in Figure 1, which shows the starting screen when running the application. There are 3 different tabpages that make up the application: Data, Fit Models and Advanced Plotting. We will discuss the different tabs accordingly.

Control data loading

Browse...
das1.rda
Upload complete

Subset of Data According to

sex

For 'sex' keep value(s)

f

Which response(s) do you want to consider?

BW

Type of Response

continuous individual

☐ Litter effect

Show 15 entries

Search:

Dose	LDH	UBH	BW	sex	food
0	1850	1	252	f	2
0	2050	1	268	f	2
0	1040	1	304	f	1
0	1100	1	258	f	2
0	910	1	256	f	2
0	1920	1	294	f	2
0	1240	1	292	f	2
0	1100	1	262	f	2
0	1480	1	258	f	2
0	1580	1	247	f	1
400	1420	1	269	f	2
400	1540	1	256	f	1
400	1680	1	274	f	1
400	1040	1	232	f	1
400	1580	1	257	f	1

Showing 1 to 15 of 40 entries

Previous 1 2 3 Next

Note: Samples containing missing values have been removed from the data.
You can select rows in the table that should be excluded from the analysis (outliers).

You have selected 1 outlier(s).

Figure 2: Subsetting data.

1.3.1 Data

In the Data-tab, data can be uploaded and subsetting as desired. Before uploading new data, the user has the option to specify the format of the data (see Figure 1). If this is not specified, the system will try to deduce the format automatically by determining the extension of the uploaded file. There are 2 ways a subset of the data can be created: either by filtering on a certain variable or by manually selecting the observations that are to be excluded from the analysis. This is illustrated in Figure 2.

Additionally, the user can choose the response(s) and the type of response(s) that need to be considered. Possible options for response type are:

- Continuous summary
- Continuous individual
- Quantal

Depending on the chosen response type, the user can indicate whether or not the data is clustered by checking the checkbox 'Litter effect' below the selection of the type of response (see Figure 2). This option has been provided for types continuous individual and quantal, but is not available for continuous summary.

Data Variables

Independent variable (e.g. dose)
Dose

Covariate
<select>

Response(s): BW

Data suitability

Responses: General estimation BW

There seems to be enough information in the dose-response data to estimate the BMD with certain level of accuracy.

Analysis

Value for CES
0.05

Probability for BMD credible interval
0.9

Prior Specification
☒ Default ☐ Informative

Distribution
☒ Normal ☒ Lognormal

Advanced Settings

Sampling
☒ Laplace approximation ☐ Bridge Sampling

Extend dose range
☒ Yes

Number of draws to be made from the posterior distribution
30000

Number of MCMC chains
3

Number of MCMC iterations
3000

Number of MCMC iterations discarded as warmup
1000

Model Weights

Figure 3: Fit models tabpage for continuous individual unclustered data.

1.3.2 Fit Models

In the Fit Models tab, further specifications can be made before running the analysis. The tab is divided in multiple sections:

- Data variables
- Data suitability
- Analysis
- Advanced Settings
- (Dose response effect)

Note that the layout of each section depends on the type of response and whether or not the data is clustered. The Dose response section is for example only available for clustered quantal data. An example of how the tabpage looks for continuous individual, unclustered data is given in Figure 3.

In each of the sections specific options can be set. Depending on the chosen response type and the clustering of the data, this includes for section Data Variables choosing:

- The independent variable
- A covariate
- The type of variation statistic
- The variable name of the variation statistic in the data
- The variable name of the sample size in the data

The Data Suitability section is only available for continuous data (either summary or individual). Here, an estimate is made regarding the feasibility of performing a BMD analysis. In the subtab General estimation, the user can see whether BMD analysis would be feasible for all selected responses or not (see Figure 3). The user is then able to determine the estimate per selected response. When there is data uploaded containing observations for which the standard deviation is larger than the mean for one of the selected responses, there is an additional warning provided in this section. When this warning is triggered, the checkbox 'Normal' of the

Distribution input in the Analysis section is automatically unchecked.

In the Analysis section the user can set:

- The value for the BMR
- The probability for the BMD credible intervals
- The prior specification
- The distribution (for continuous data)

When an informative prior is selected, prior specification inputs are shown related to background, maximum fold change, BMD parameter and the prior distribution (Figure 4). For quantal data, these options are limited to the background, BMD parameter and the prior distribution. When a covariate has been selected, only the prior distribution option is provided.

Prior Specification

☐ Default ☒ Informative

Model parameters

Natural parameters

Background ☒ Shape Parameter

Minimum	Most likely	Maximum
<input type="text" value="0.001"/>	<input type="text" value="10.87"/>	<input type="text" value="21.74"/>

Natural parameters

Prior BMD ☐ Shape Parameter

Minimum	Most likely	Maximum
<input type="text" value="0"/> ✓ Value 0 is internally transformed to 2.23e-306 for calculation	<input type="text" value="50"/>	<input type="text" value="10000"/>

Natural parameters

Maximum/minimum response ☒ Shape Parameter

Minimum	Most likely	Maximum
<input type="text" value="12.07"/>	<input type="text" value="55.43"/>	<input type="text" value="110.86"/>

Technical parameters

Prior d

Distribution

☒ Normal ☒ Lognormal

Figure 4: Prior specification inputs in the Analysis section of the Fit Models tab.

Advanced Settings

Sampling

☒ Laplace approximation

☐ Bridge Sampling

Extend dose range

☒ Yes

Number of draws to be made from the posterior distribution

30000

Model Weights

	Model	Weights
1	Exponential Normal	1.00
2	Inverse Exponential Normal	1.00
3	Hill Normal	1.00
4	Lognormal Normal	1.00
5	Gamma Normal	1.00
6	Quadratic Exponential Normal	1.00
7	Probit Normal	1.00
8	Logit Normal	1.00
9	Exponential Lognormal	1.00
10	Inverse Exponential Lognormal	1.00
11	Hill Lognormal	1.00
12	Lognormal Lognormal	1.00
13	Gamma Lognormal	1.00
14	Quadratic Exponential Lognormal	1.00
15	Probit Lognormal	1.00
16	Logit Lognormal	1.00

Figure 5: Advanced Settings section in the Fit Models tab.

In the Advanced Settings (Figure 5), the user can set the:

- Sampling methodology
- Option to extend the dose range
- Number of draws from the posterior distribution
- Number of MCMC chains
- Number of MCMC iterations
- Number of MCMC iterations to be discarded as warmup
- Model weights

The user can change the model weights by left clicking the weight of the model that needs to be changed and typing the desired weight for that model. When a covariate has been selected, these options are limited to the sampling methodology, extending the dose range, the number of draws from the posterior distribution and the model weights.

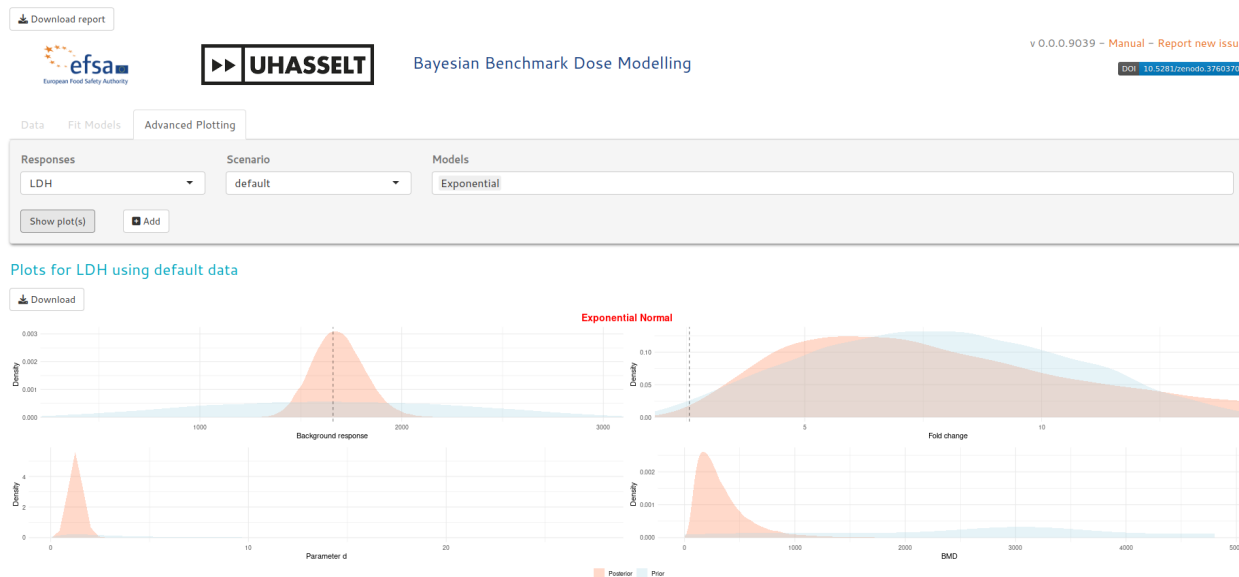


Figure 6: Advanced Plotting tab, with example prior and posterior distribution parameter estimate plot.

1.3.3 Advanced Plotting

This tab is only available after running the analysis without selecting a covariate. It provides the user the option to plot and download the prior and posterior distribution of parameter estimates (Figure 6). When multiple responses or analyses have been performed, the user can select the plots over different responses and analysis scenarios by adding a new row of inputs to the input panel.

1.4 Report

A Word report of the performed analysis can be downloaded by clicking the **Download report**-button in the top left corner of the application. This report contains the inputs used for the analysis, justifications for deviating from default values and the different outputs.

1.5 Output

After clicking the button Fit Model(s) at the bottom of the Fit Models tab, the user has the option to provide their email address where a notification will be sent to when the output is ready. The analysis starts after the Start button is pressed (Figure 7).

Start Analysis

If you would like to receive an email with the analysis results when finished, please provide an e-mail address.
Leave empty if you don't want to receive notifications.

Email address

Identifier for your analysis

X Cancel

✓ Start

Figure 7: Pop-up window after the Fit Model(s) button has been pressed.

During the analysis, the application internally performs various tests on the data used for analysis. Depending on the outcome of certain tests, additional sensitivity analyses are performed and shown in the output. The type and amount of tests that are performed are related to the type of response that is selected by the user and the indicated clustering of the data. The performed tests for each response type are listed below.

Continuous summary (see Figure 8):

- Check for dose-response effect
- Check for constant variance coefficient of variation (using Bartlett test)
- Goodness of fit (with Bayes factor value)

Continuous individual:

- Shapiro-Wilk normality test
- Check for dose-response effect
- Check for constant variance coefficient of variation (using Bartlett test and Levene's test)
- Goodness of fit (with Bayes factor value)

Quantal:

- Check for dose-response effect
- Goodness of fit (with Bayes factor value)

When an analysis is run with a covariate, no additional tests are performed. When there is no evidence for a dose-response effect, the output of the tables and plots are blocked. Flowcharts describing the performed analyses for response types continuous summary and continuous individual are added in the appendices of this document (Appendices Figures 17-21). When the analysis is done, the output appears at the bottom of the Fit Models tab. Depending on the amount of selected responses, there will be multiple panels in the navigation bar showing the output of each response (see Figure 8). In the dropdown menu of each response, the outputs of the additional analyses described above are shown.

The next output is a table containing a summary of the fitted model-averaged model (Figure 9). In this table, the type of BMD model (Model Averaged), type of sampling (Laplace or Bridge sampling), BMD lower limit,

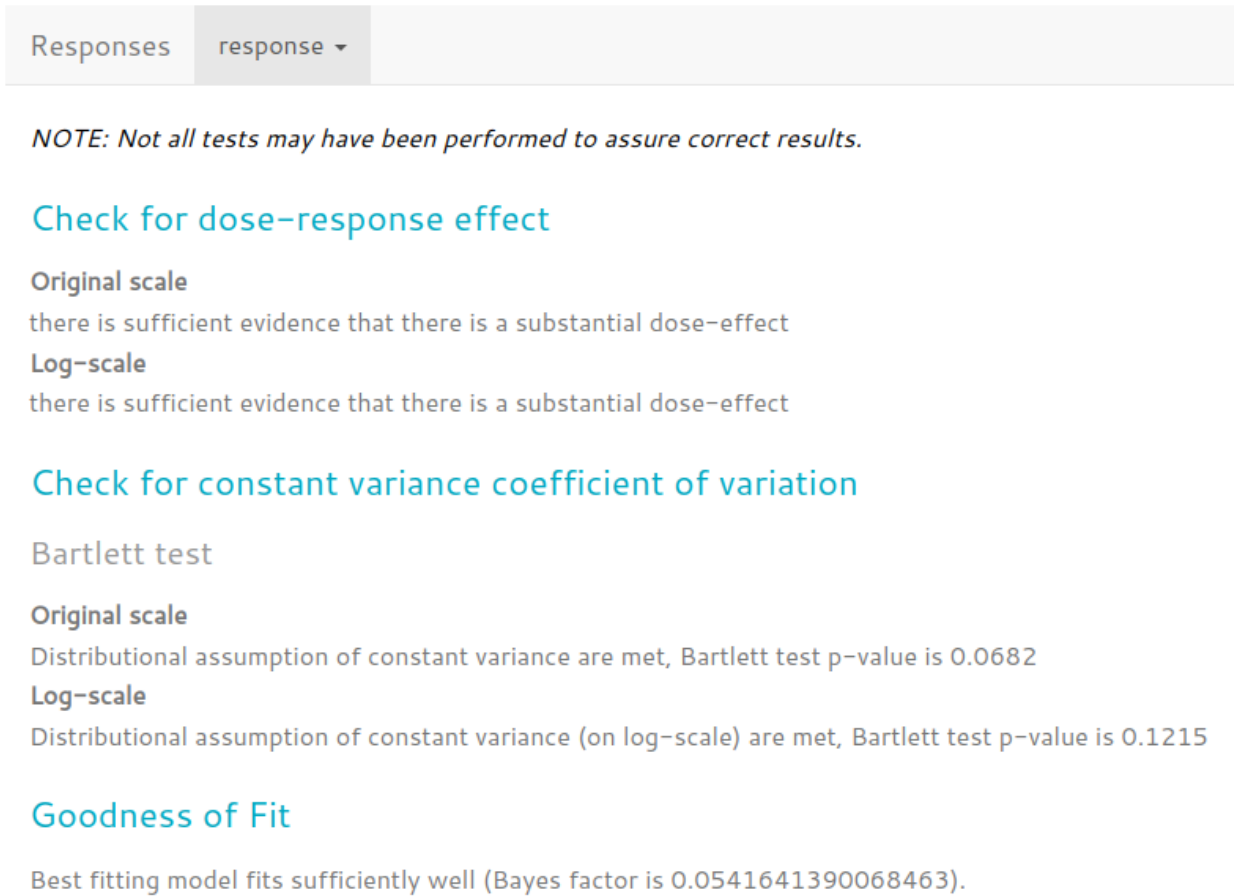


Figure 8: Navigation bar displaying the selected response(s) and the performed tests (for response type continuous summary).

Fitted Models

Full Laplace

Model Averaged BMD

Download ▾

	Model	Type	BMDL	BMD	BMDU
default	Model Averaged	LP	11.201	31.702	84.651

Showing 1 to 1 of 1 entries

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1

Next

Note: analyses with no violations are highlighted in green. When assumptions/checks have been violated, the analysis is highlighted in red.

Figure 9: Table containing summary of the fitted model(s).

BMD upper limit and the mean BMD values can be read. When additional analyses have been performed in accordance with the tests described above, the fitted models as an output of these analyses are shown in this table as well. Models that were made using data that violated the implemented tests are shown in red in the table, while models that don't have any violations are shown in green.

Figure 10 shows the second table of the output: this table contains the BMDL, BMDU and BMD of each of the individually fitted models along with the weights used for model-averaging. Both tables can be downloaded as .csv files via the provided **Download** button.

Finally, Figures 11-16 show different plots of the fitted models, which can all be downloaded individually via the Download button.

2 APPENDICES

Estimated BMDs per model

Download ▾

	Model	BMDL	BMD	BMDU	Model Weights
1	E4_N	15.009	42.866	122.122	0
2	IE4_N	47.018	76.63	124.66	0
3	H4_N	14.84	41.86	119.607	0
4	LN4_N	18.927	56.398	170.885	0
5	G4_N	15.794	39.699	98.303	0
6	QE4_N	6.959	17.856	46.132	0
7	P4_N	15.757	45.645	128.553	0
8	L4_N	16.059	46.206	131.151	0
9	E4_LN	13.525	35.807	95.314	0.1
10	IE4_LN	19.555	41.303	87.765	0.114

Showing 1 to 10 of 16 entries

Previous

1

2

Next

Note: Numeric values are rounded to 3 decimals.

Figure 10: Table showing the model weights of the different fitted models.

Plots

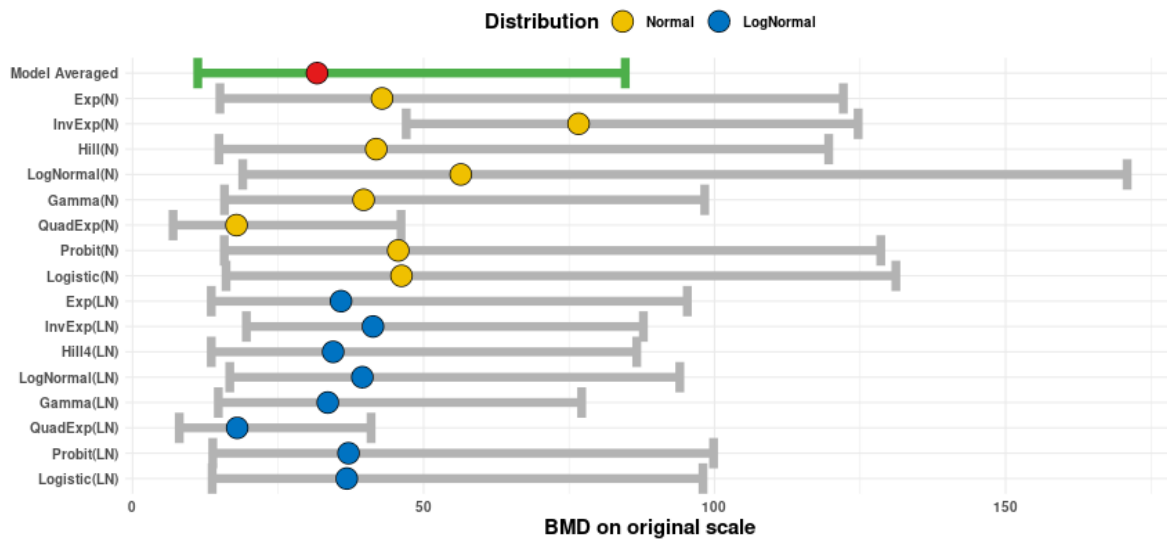
[Download](#)


Figure 11: Plot showing the BMD on the original scale over the fitted models (including Model Averaged).

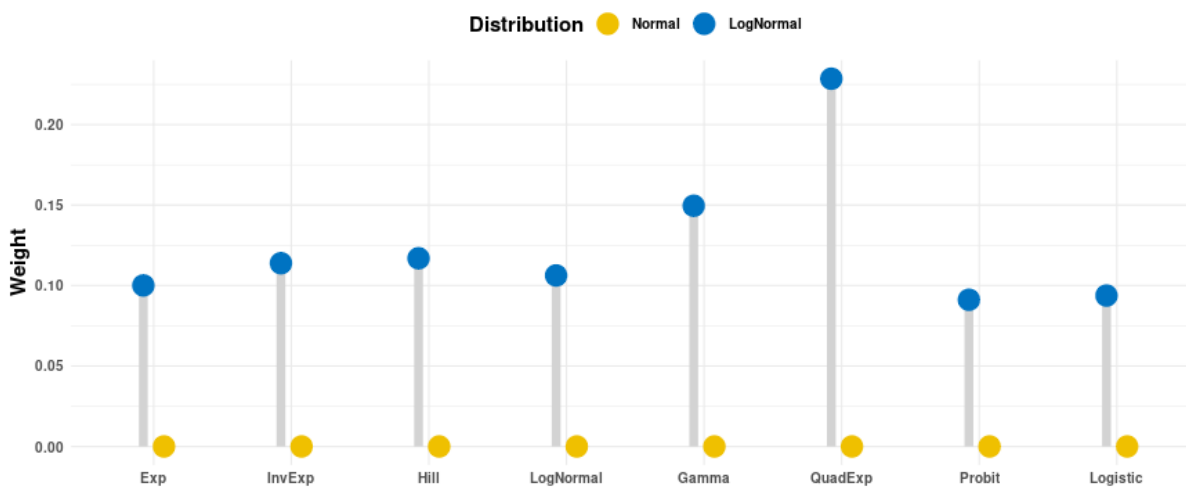
[Download](#)


Figure 12: Plot showing weights used for averaging for every fitted model.

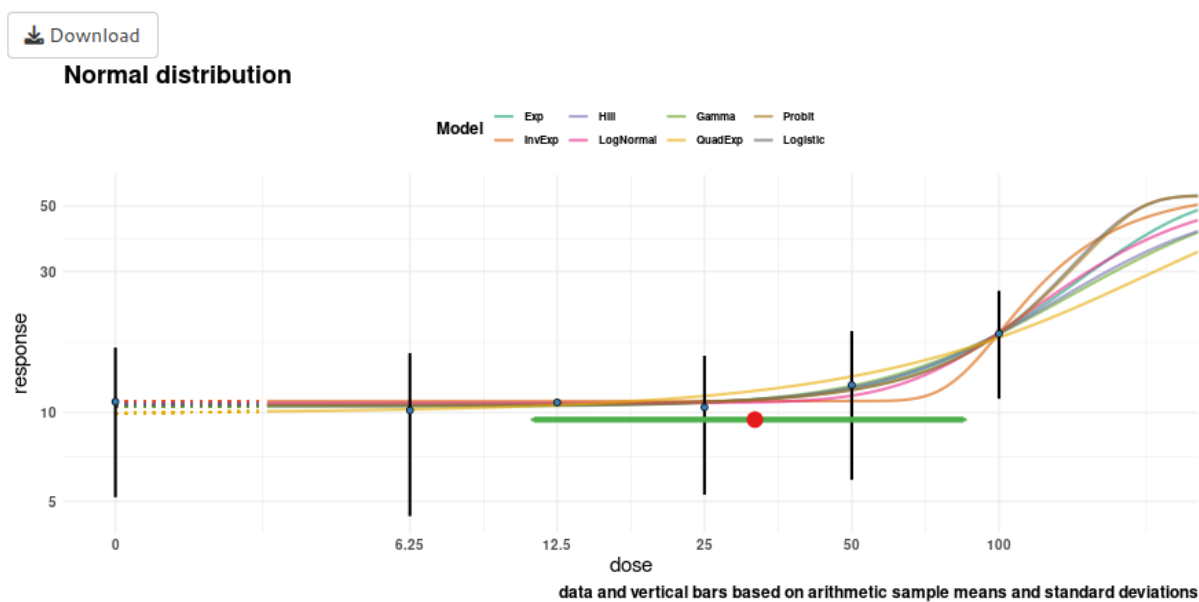


Figure 13: Fit of each normal model through the datapoints used for analysis.

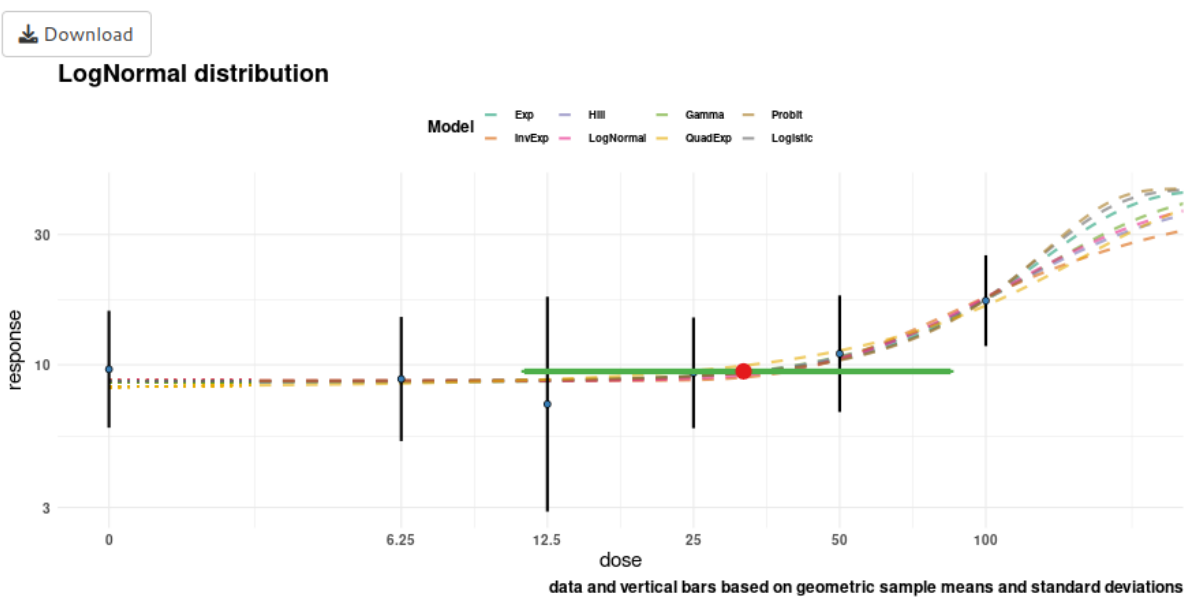


Figure 14: Fit of each lognormal model through the datapoints used for analysis.

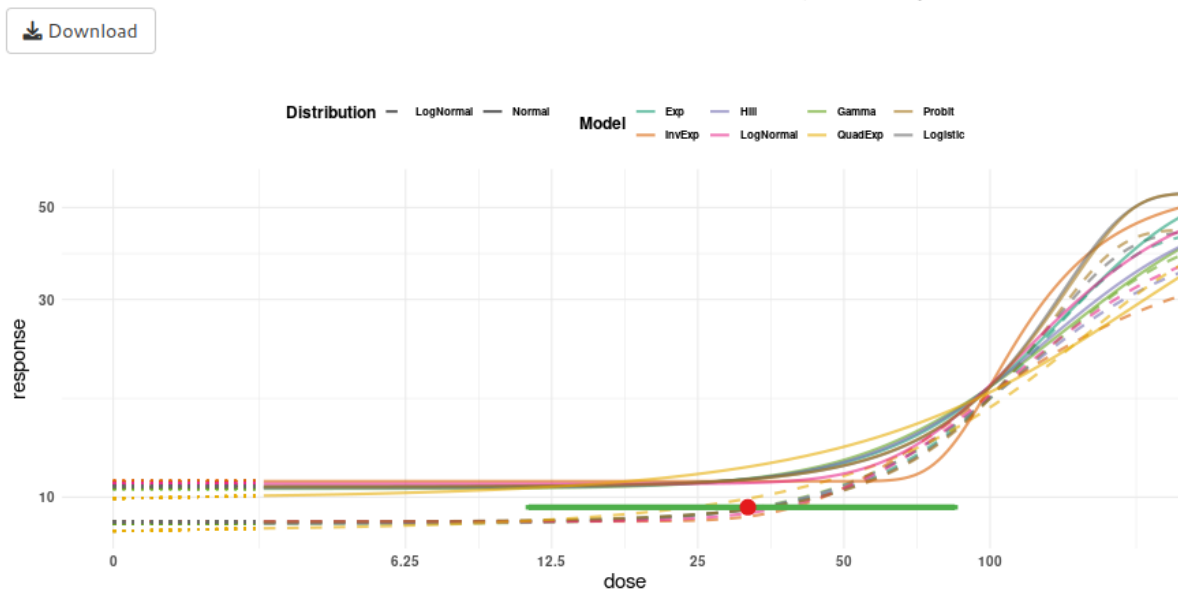


Figure 15: Fit of each normal and lognormal model through the datapoints used for analysis.

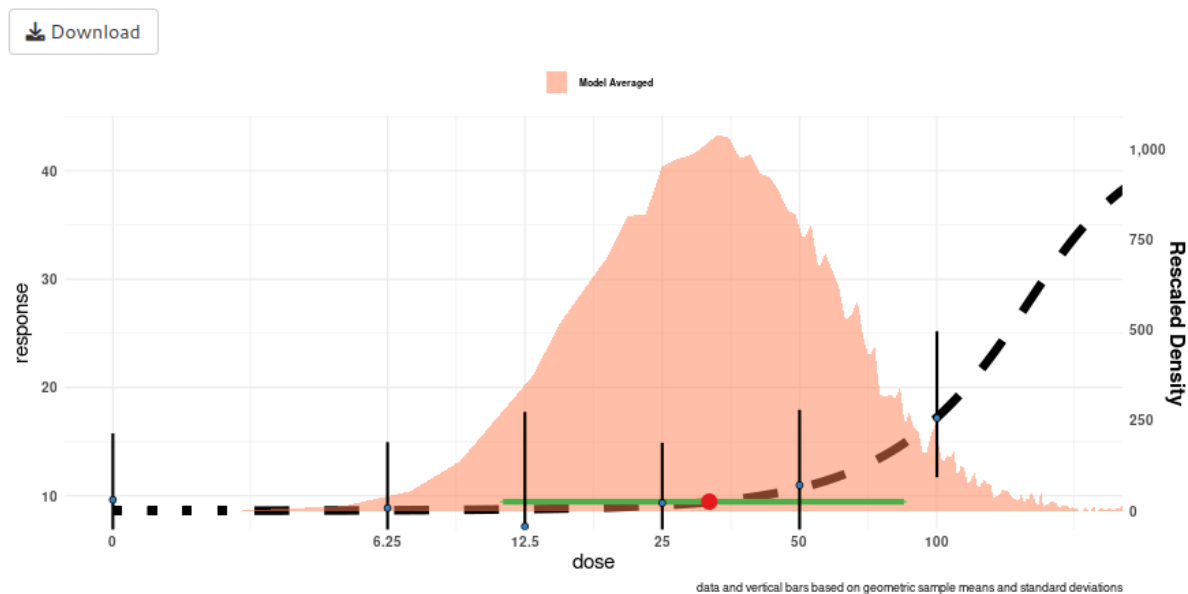


Figure 16: Fitted BMD response of the Model Averaged model.

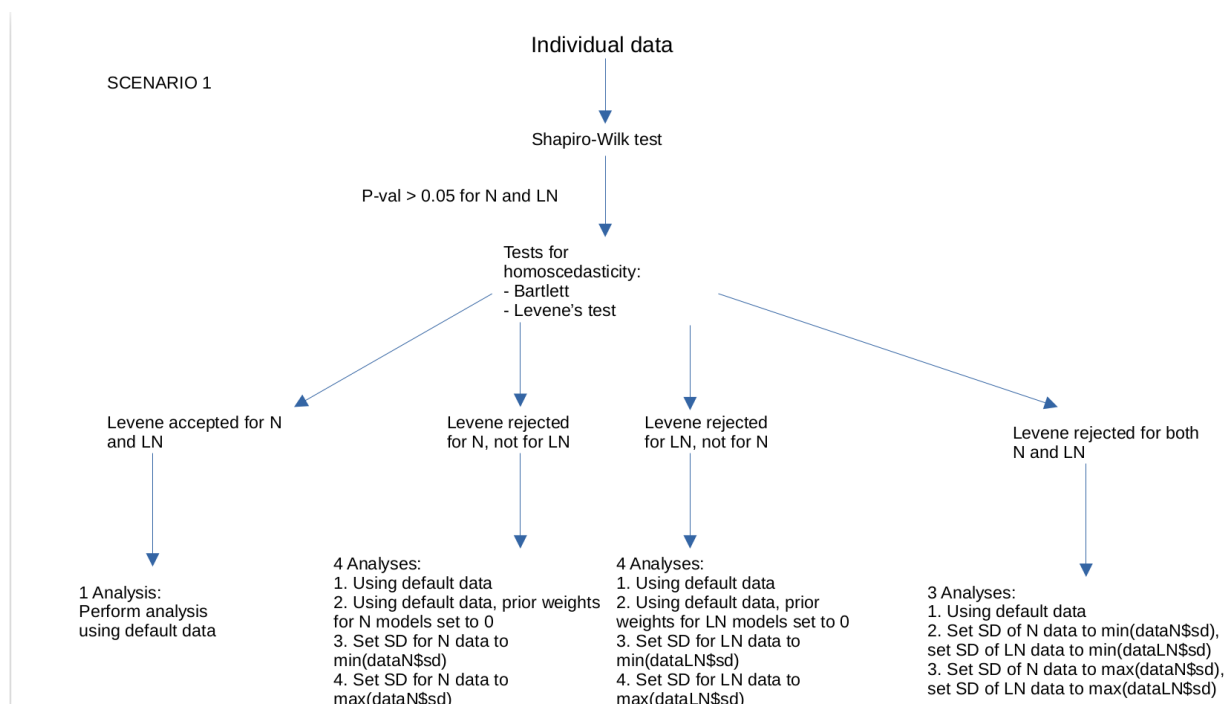


Figure 17: Flowchart for response type: continuous summary.

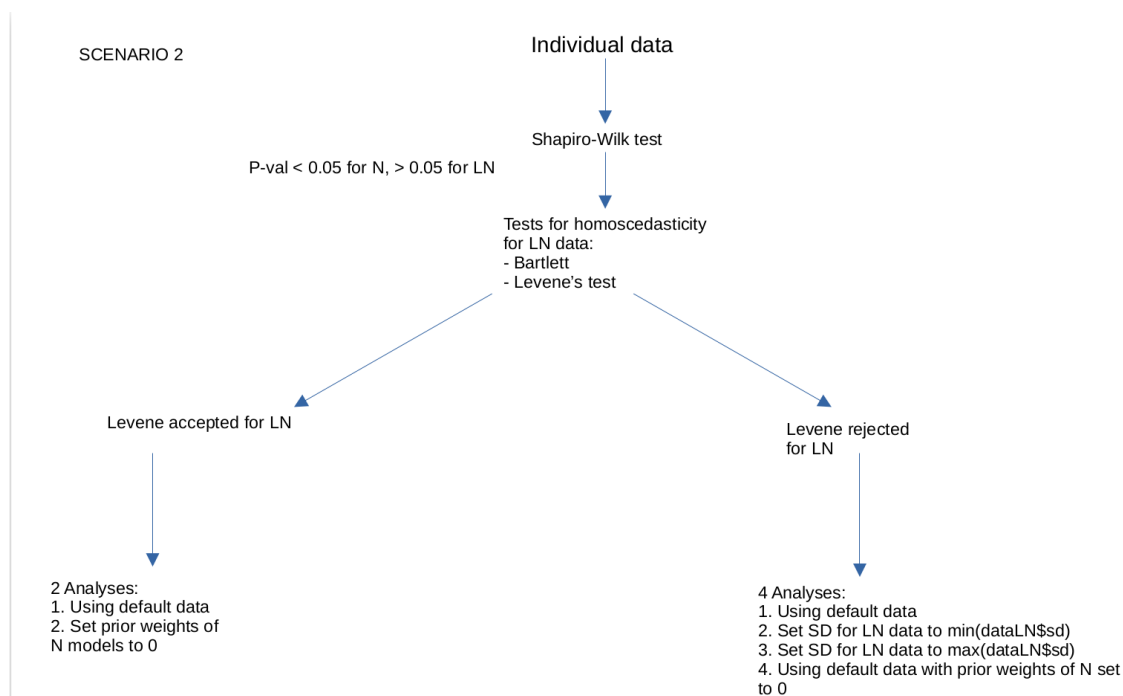


Figure 18: Flowchart for response type: continuous individual (scenario 1).

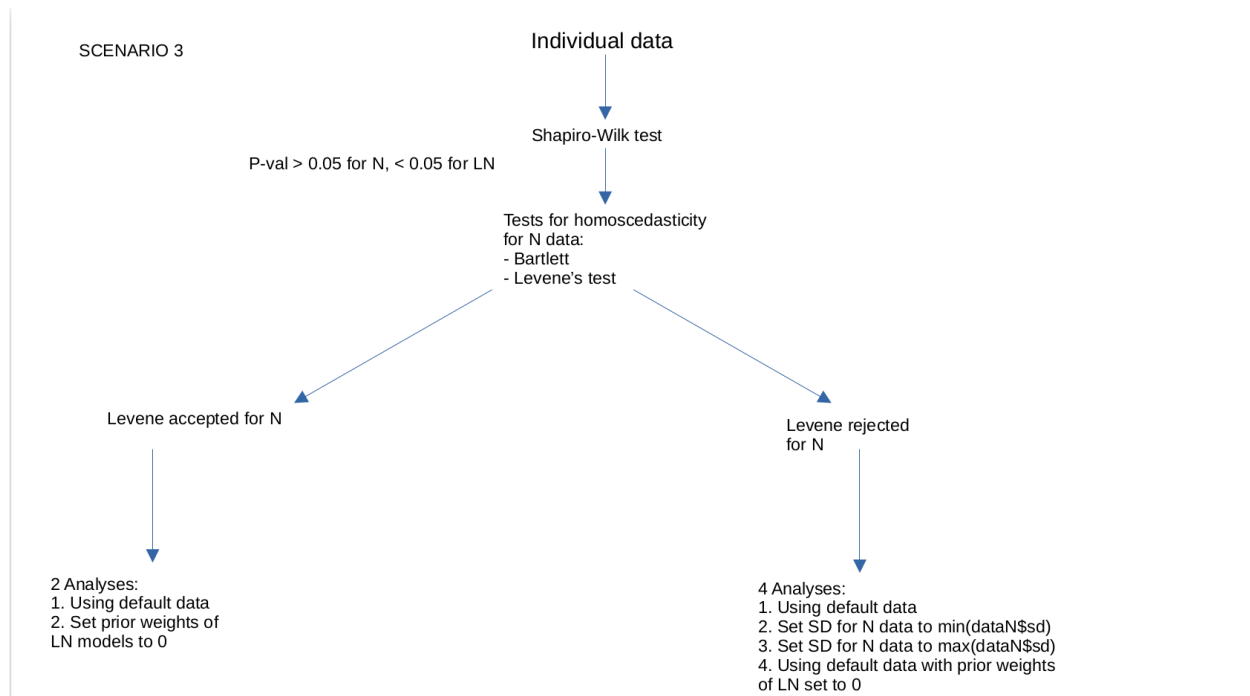


Figure 19: Flowchart for response type: continuous individual (scenario 2).

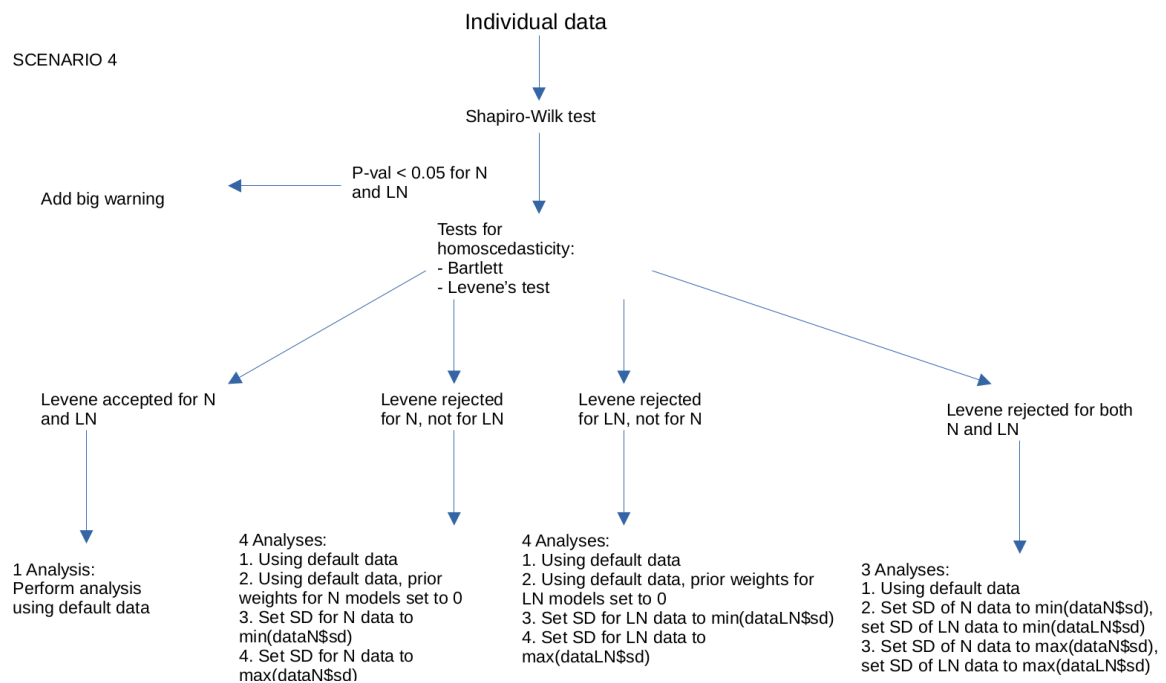


Figure 20: Flowchart for response type: continuous individual (scenario 3).

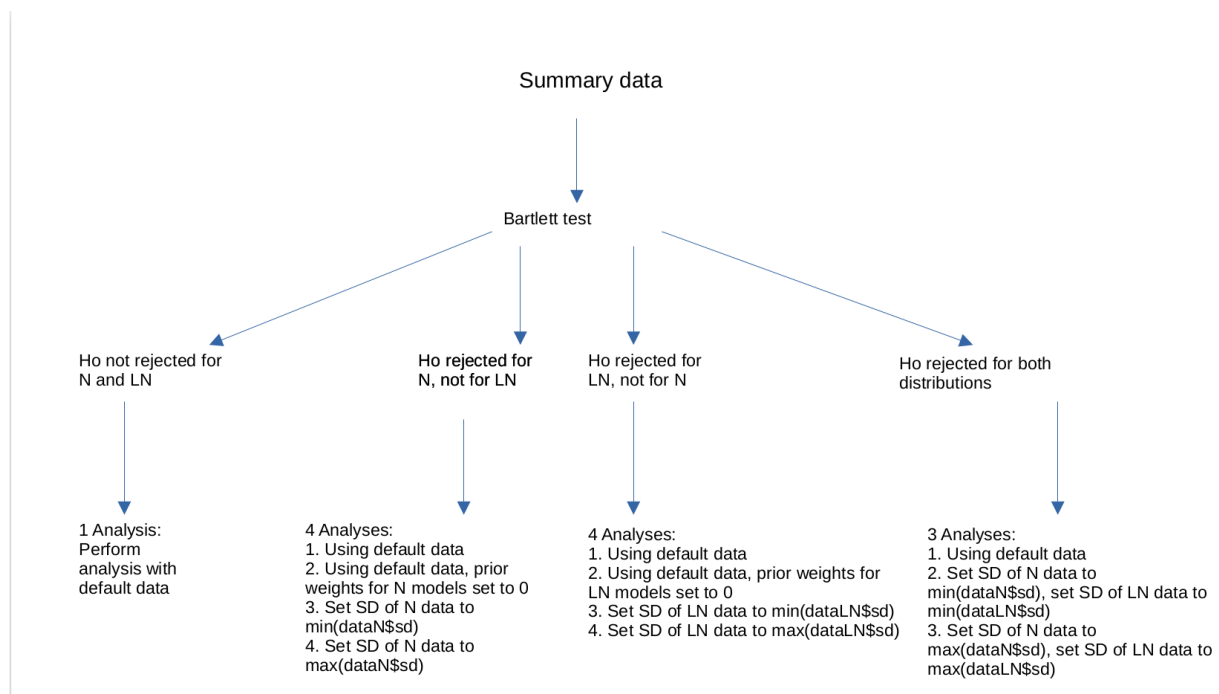


Figure 21: Flowchart for response test type: continuous individual (scenario 4).